Synopsis – Study 15905A

Study Title An interventional, randomised, double-blind, parallel-group, placebo-controlled study on the efficacy of vortioxetine on cognitive dysfunction in patients with partial or full remission of major depressive disorder
Investigators 17 principal investigators at 17 sites in 5 countries *Signatory investigator* – [redacted]
Study Sites 17 sites – 2 in Estonia, 6 in Finland, 5 in Germany, 2 in Serbia, and 2 in Slovakia
Publications None (as of the date of this report)
Study Period *First patient first visit* – 20 October 2014 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 25 April 2016 (the date of the last protocol-specified contact with any patient)
Objectives • *Primary objective*: – to assess the efficacy of vortioxetine (10 to 20 mg/day) as adjunctive treatment to stable SSRI dose *versus* stable SSRI monotherapy on cognitive performance (focusing on the aspect concerning speed of processing, executive functioning and attention) in patients who are in partial or full remission from their Major Depressive Episode (MDE). • *Secondary and exploratory objectives*: – to assess the efficacy of vortioxetine as adjunctive treatment to stable SSRI dose *versus* stable SSRI monotherapy on: • cognitive dysfunction (performance and subjective reporting) • depressive symptoms • clinical global impression • functionality – to assess the efficacy of vortioxetine as adjunctive treatment to stable SSRI dose *versus* vortioxetine as monotherapy on: • cognitive dysfunction (performance and subjective reporting) • depressive symptoms • clinical global impression • functionality – to assess the efficacy of vortioxetine as monotherapy *versus* stable SSRI monotherapy on: • cognitive dysfunction (performance and subjective reporting) • depressive symptoms • clinical global impression • functionality – to assess the safety and tolerability of vortioxetine as monotherapy and as adjunctive treatment to SSRIs.

Study Methodology

- This was an exploratory, interventional, prospective, multi-national, multi-site, randomised, double-blind, parallel-group, placebo-controlled, flexible-dose study.
- The study consisted of:
  - a 4 to 10-day Screening Period (from screening to randomisation)
  - an 8-week Core Treatment Period
  - a 4-week Safety Follow-up Period, of which the first week was a taper-down period
- At Baseline, the patients were randomised equally (1:1:1) to double-blind treatment with current stable selective serotonin re-uptake inhibitor (SSRI) dose and vortioxetine 10 to 20 mg/day (vortioxetine adjunctive treatment group), current stable SSRI dose and placebo (SSRI monotherapy group), or vortioxetine 10 to 20 mg/day and placebo (vortioxetine monotherapy group). Patients randomised to treatment with vortioxetine and placebo discontinued their current SSRI monotherapy at baseline.
- For patients randomised to treatment with vortioxetine, the initial treatment dose of vortioxetine was 10 mg/day. Based on the investigator judgement there was a possibility to increase the dose with a 10 mg increment to 20 mg/day at Week 1. For patients who did not tolerate the increased dose, the investigator could decrease the dose at Week 2 or Week 4. The dose of vortioxetine could not be increased above 20 mg/day or decreased below 10 mg/day. After the end of Week 4, the dose had to remain fixed. For patients who were randomised to continued SSRI treatment during the 8-week Core Treatment Period, the SSRI dose was the same as that at inclusion.
- Patients who completed the 8-week, double-blind Core Treatment Period had the option to enter a 1-week, double-blind, taper-down period: patients treated with vortioxetine received placebo; patients treated with higher doses of SSRIs (15 or 20 mg escitalopram, 30 or 40 mg citalopram, or 150 or 200 mg sertraline) received lower doses (10 mg escitalopram, 20 mg citalopram, or 100 mg sertraline). Patients who did not enter the optional taper-down period were treated at the investigator's discretion.
- During the Core Treatment Period, patients were seen at Weeks 1, 2, 4, and 8, at which efficacy and safety data were collected; at Week 6, the investigator contacted the patient directly by phone, in order to verify the patient's health status.
- Patients who withdrew were seen for a Withdrawal Visit as soon as possible. Treatment with the 1-week, double-blind, down-taper medication was to be offered to patients who withdrew.
- A Safety Follow-up Visit/contact was performed approximately 4 weeks after the Completion/Withdrawal Visit.

Number of Patients Planned

150 patients were planned for randomisation: 50 in the SSRI/vortioxetine group, 50 in the SSRI/placebo group, and 50 in the vortioxetine/placebo group.

Diagnosis and Main Selection Criterion

In- or outpatients who had achieved either partial (some symptoms of a MDE are present but full criteria are not met) or full remission of major depressive disorder (MDD), diagnosed according to DSM-IV-TR™ criteria, who:

- had a Hamilton Depression Rating Scale 17-items ($HAM\text{-}D_{17}$) total score ≤10 at the Screening Visit and at the Baseline Visit
- had received SSRI monotherapy for the MDE from which they were in full or partial remission for ≥12 weeks at licensed doses and been on stable dose ≥8 weeks prior to the Screening Visit
- had a ≥50% response to current SSRI treatment, as assessed using the Antidepressant Treatment Response Questionnaire (ATRQ)
- had a Perceived Deficits Questionnaire – Depression (PDQ-D) total score >25
- were ≥18 and ≤65 years of age

Investigational Medicinal Products, Doses and Mode of Administration, Batch Numbers

Vortioxetine – 10 or 20 mg/day; encapsulated tablet, orally; batch No. 2391955 (10 mg) and 2373931 (20 mg)

Reference Therapies, Doses and Mode of Administration, Batch Numbers

Placebo – powder-filled capsules, orally; batch No. E08765-001E

Escitalopram – 5, 10, 15, or 20 mg/day; encapsulated tablets, orally; batch No. 2381948 (5 mg), 2389938 (10 mg), 2382222 (15 mg), and 2388070 (20 mg)

Citalopram – 10, 20, 30, or 40 mg/day; encapsulated tablets, orally; batch No. 2385633 (10 mg), 2381043 (20 mg), 2370341 (30 mg), and 2379181 (40 mg)

Sertraline – 50, 100, 150, or 200 mg/day; encapsulated tablets, orally; batch No. XT5014007-A (50 mg), XT1014003-A (100 mg), XT5014007-A and XT1014003-A (150 mg), and XT1014003-A (200 mg)

Duration of Treatment

8 weeks of treatment followed by a 1-week optional double-blind down-taper period

Efficacy Assessments

- Neuropsychological tests and performance-based functionality
  - Digit Symbol Substitution Test (DSST)
  - Rey Auditory Verbal Learning Test (RAVLT)
  - Trail Making Test A (TMT-A)
  - Trail Making Test B (TMT-B)
  - Stroop Colour Naming Test (STROOP)
  - Simple Reaction Time (SRT)
  - Choice Reaction Time (CRT)
  - University of San Diego Performance-based Skills Assessment – Brief (UPSA-B)
- Patient-reported cognitive function
  - Perceived Deficits Questionnaire – Depression (PDQ-D)
- Depressive symptoms, clinical global impression, and functionality
  - Hamilton Depression Rating Scale 17-items ($HAM\text{-}D_{17}$)
  - Clinical Global Impression – Severity of Illness (CGI-S)
  - Clinical Global Impression – Global Improvement (CGI-I)
  - Functioning Assessment Short Test (FAST) – Clinician-rated
  - Sheehan Disability Scale (SDS) – patient reported
- Patient-reported positive affect
  - Clinical Positive Affect Scale – Self-Rated (CPAS-SR)

Pharmacokinetic Assessments

- blood sampling for plasma quantification of vortioxetine, escitalopram, citalopram, and sertraline (reported separately)

Genomic/Metabolomic/Proteomic Assessments

- blood sampling for gene expression profiling
- blood sampling for metabolomic/proteomic biomarkers
- blood sampling for pharmacogenetics

The results of the genomic and metabolomic/proteomic assessments are not included in this *Clinical Study Report*

Safety Assessments

- Adverse events (AEs), clinical safety laboratory tests, vital signs, weight/BMI, electrocardiograms (ECGs), and physical examinations
- Columbia Suicide Severity Rating Scale (C-SSRS)

Endpoints

- *Primary Endpoint*
  - cognitive performance:
    - change from baseline to Week 8 in DSST (number of correct symbols)
- *Key Secondary Endpoint*
  - functionality, performance-based:
    - change from baseline to Week 8 in UPSA-B total score
- *Secondary Endpoint*
  - cognitive dysfunction, neuropsychological tests:
    - change from baseline to Week 8 in RAVLT scores (acquisition: learning; delayed recall: memory)
    - change from baseline to Week 8 in TMT scores (TMT-A: speed of processing; TMT-B: executive functioning)
    - change from baseline to Week 8 in reaction time scores (SRT: psychomotor speed; CRT: attention)
    - change from baseline to Week 8 in STROOP score (congruent score: speed of processing; incongruent score: executive functioning)
    - overall cognition composite score (including all neuropsychological tests) – change from baseline to Week 8 in the composite z-score defined as the equally weighted sum of the z-scores of the DSST, RAVLT, TMT-A, TMT-B, STROOP, SRT, and CRT
  - cognitive dysfunction, patient-reported:
    - change from baseline to Week 8 in PDQ-D total score
  - depressive symptoms and global clinical impression
    - change from baseline to Week 8 in HAM-D_{17} total score
    - change from baseline to Week 8 in CGI-S
    - CGI-I score at Week 8
- *Exploratory Endpoints*
  - Change from baseline to all visits where assessed, in addition to those mentioned above, in the neuropsychological tests (DSST, RAVLT, TMT-A, TMT-B, STROOP, SRT, CRT), overall cognition composite score (including all neuropsychological tests), PDQ-D total score and subscale scores, HAM-D_{17} total score, CGI-S score, FAST total score, SDS total and subscale scores, and CPAS-SR score
  - CGI-I score at all visits where assessed
- *Safety Endpoints*
  - adverse events
  - absolute values and changes from baseline in clinical safety laboratory tests, vital signs, weight, and ECG parameters
  - potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values
  - C-SSRS categorisation based on Columbia Classifica Algorithm for Suicide Assessment (C-CASA) definitions (1, 2, 3, 4 and 7)

Statistical Methodology

- The following analysis sets were used
  - *all-patients-randomised set* (APRS) – all randomised patients
  - *all-patients-treated set* (APTS) – all patients in the APRS who took at least one dose of double-blind IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of the DDST (number of correct symbols)
- Unless otherwise indicated, the efficacy analyses were based on the FAS and the safety analyses were based on the APTS.
- The treatment effects for all efficacy scores were standardized allowing for comparisons of the magnitude of the effect sizes between different endpoints. These standardized effect sizes were calculated for differences from placebo using the least square means and the standard errors from the linear models.
- *Analyses of the Primary Endpoint*
  - The primary endpoint was analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). The model included site group, week (Weeks 1 to 8), and treatment as fixed effects, baseline score as a continuous covariate, treatment-by-week interaction, and baseline score-by-week interaction. An unstructured covariance structure was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The analysis was based on the missing-at-random (MAR) assumption and performed using all available observations (observed cases [OC] data) in the Treatment Period.
  - All three treatment contrasts were estimated at each visit based on the least squares means for the treatment-by-visit interaction in the MMRM-model. The estimates are presented with p-values and 95% CIs.
  - Sensitivity analyses were performed to evaluate how different assumptions affect the estimates of the treatment effect.
  - A sensitivity analysis of the primary endpoint was performed using an analysis of covariance (ANCOVA) by week using the last observation carried forward (LOCF) and observed cases (OC), including site group and treatment as fixed effects, and baseline score as a continuous covariate. The mean difference between vortioxetine as adjunctive treatment to stable SSRI and stable SSRI monotherapy was estimated from the model based on the least squares means for treatment. The estimates are presented with p-values and 95% CIs.
- *Analysis of the Key Secondary Efficacy Endpoint*
  - The key secondary endpoint, change from baseline to Week 8 in UPSA-B total score, was analysed with an ANCOVA model. The analysis was based on the last observation carried forward (LOCF) and include site group and treatment as factors and baseline UPSA-B total score as a continuous covariate.
  - The mean differences between treatment groups were estimated based on the least squares means for the treatment factor in the ANCOVA-model. The estimates were presented with p-values and 95% CIs.
  - A sensitivity analysis of the key secondary endpoint was performed using the same ANCOVA model as specified above, but excluding patients with a baseline UPSA-B total score of 100, since this is the maximal obtainable score in UPSA-B.
  - A sensitivity analysis of the key secondary endpoint, change from baseline to Week 8 in UPSA-B total score, was performed with an ANCOVA model using observed data (OC), including site group and treatment as factors, and baseline UPSA-B total score as a continuous covariate. The mean difference will be estimated from the model based on the least squares means for treatment.
- *Testing Strategy*
  - A hierarchical testing strategy was defined *a priori* in the *Statistical Analysis Plan* and comprised the primary endpoint, as well as the key secondary efficacy endpoint. The testing continued as long as significance was obtained at 5% at each step of the hierarchy.
  - The following sequence of hierarchically ordered primary and key secondary endpoints was used:
  - 1. change from baseline to Week 8 in DSST (number of correct symbols) using MMRM (primary endpoint) – comparison between vortioxetine as adjunctive treatment to stable SSRI dose *versus* stable SSRI monotherapy

Statistical Methodology (continued)

- 2. change from baseline to Week 8 in UPSA-B total score, using ANCOVA, LOCF (key secondary endpoint) – comparison between vortioxetine as adjunctive treatment to stable SSRI dose *versus* stable SSRI monotherapy
- 3. change from baseline to Week 8 in DSST number of correct symbols using MMRM (primary endpoint) – comparison between vortioxetine as monotherapy *versus* stable SSRI monotherapy
- 4. change from baseline to Week 8 in UPSA-B total score, using ANCOVA, LOCF (key secondary endpoint) – comparison between vortioxetine as monotherapy *versus* stable SSRI monotherapy

• *Analysis of the Secondary Endpoints*

- Three different comparisons were made for the secondary endpoints:
  - vortioxetine as adjunctive treatment to stable SSRI dose *versus* stable SSRI monotherapy
  - vortioxetine as adjunctive treatment to stable SSRI dose *versus* vortioxetine as monotherapy
  - vortioxetine as monotherapy *versus* stable SSRI monotherapy.
- The continuous and categorical secondary endpoints were analysed using a MMRM model similar to the model specified for the primary endpoint. The continuous and categorical secondary endpoints were also analysed using an ANCOVA (OC and LOCF) model similar to the model specified for the sensitivity analysis for the primary analysis

• *Analysis of Exploratory Endpoints*

- As for the secondary efficacy endpoints, comparisons between all three treatments were made for the exploratory endpoints.
- The continuous and categorical exploratory endpoints were analysed using a MMRM model similar to the model specified for the primary endpoint. The continuous and categorical exploratory endpoints were also be analysed using an ANCOVA (OC and LOCF) model similar to the model specified for the primary endpoint.
- Association between functionality (FAST, UPSA-B) and endpoints addressing cognitive dysfunction (DSST, TMT-A, TMT-B, STROOP, RAVLT, SRT, CRT, PDQ-D) were done for Week 8 assessments by means of estimation of a partial correlation coefficient, where the set of controlling variables included treatment group and baseline values for the respective variables. Association for the same outcomes at baseline were done with Pearson's correlation coefficient.
- Improvement in depressive symptoms can confound/mediate treatment effects on cognitive dysfunction, especially in subjective measures. To obtain an estimate of the degree to which the effect of treatment on the cognitive performance variables (DSST, TMT-A, TMT-B, STROOP, RAVLT, SRT, CRT) and the overall cognition composite score could be attributed to further alleviation of depressive symptoms, a HAM-D_{17} adjusted analysis was performed by adding the change from baseline in HAM-D_{17} total score at Week 8 as a covariate in the ANCOVA model. The baseline value for the HAM-D_{17} total score was also added to the model as a covariate.

• *Safety Endpoints*

- Adverse events, clinical safety laboratory tests, vital signs, weight, ECG parameters, and C-SSRS data were summarised using descriptive statistics.

Patient Disposition and Analysis Sets

• Patient disposition is summarised below:

	VOR 10-20mg		SSRI		VOR 10-20 + SSRI		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomised	50		49		52		151	
Patients treated (all-patients-treated set [APTS])	50		49		52		151	
Patients completed	47	94.0	44	89.8	47	90.4	138	91.4
Patients withdrawn	3	6.0	5	10.2	5	9.6	13	8.6
Primary reason for withdrawal:								
Adverse event(s)	1	2.0	2	4.1	3	5.8	6	4.0
Lack of efficacy	0		1	2.0	0		1	0.7
Other	2	4.0	2	2.0	1	1.9	3	2.0
Analysis sets:								
APTS	50		49		52		151	
Full-analysis set (FAS)	50		49		51		150	

Demography and Baseline Characteristics of the Study Population

- The treatment groups were comparable with respect to age, sex, and race. The overall mean age of the patients was 48 years, varying 2 to 5 years between treatment groups; 72% were women and all patients were White.
- There were no relevant differences between the treatment groups in social history (level of education, marital or employment status, and living arrangements), alcohol and smoking consumption habits, family psychiatric history, or traumatic life events.
- All patients had had at least one previous MDE and the overall mean number of previous episodes was 2.3, with a range from 1 to 8. At baseline, the mean duration of the current MDE was 87 weeks, ranging from 15 to 595 weeks for the individual patients.
- The mean baseline efficacy scores were generally comparable across the treatment groups. The mean HAM-D_{17} score of 5.8 points indicated that patients were in full or partial remission and the mean CGI-S score of 2.1 points indicated that patients were *borderline* to *mildly ill*. The mean baseline PDQ total score of 38 (on a scale from 0 to 80), indicated *moderate* cognitive symptoms as perceived by the patients.

Efficacy Results

Primary and Key Secondary Endpoints

- The results of the testing strategy are summarised below:

Endpoints	Difference to SSRI Monotherapy at Week 8 (FAS)			
	Mean	95% CI	p-value	Effect Size[a]
Primary endpoint				
ΔDSST score: vortioxetine adjunctive treatment *versus* SSRI monotherapy	-0.05[b]	-3.17; 3.08	0.9769[c]	-0.006
Key secondary endpoints				
ΔUPSA-B total score: vortioxetine adjunctive treatment *versus* SSRI monotherapy	0.96[d]	-1.77; 3.69	0.4877	0.143
ΔDSST score: vortioxetine monotherapy *versus* SSRI monotherapy	0.16[b]	-2.98; 3.30	0.9191	0.021
ΔUPSA-B total score: vortioxetine monotherapy *versus* SSRI monotherapy	1.71[d]	-1.04; 4.46	0.2212	0.252

a Standardised effect size was calculated as the difference to SSRI monotherapy. A positive value indicated that performance improved in favour of vortioxetine
b MMRM
c The testing strategy stopped; p-values are nominal.
d ANCOVA, LOCF

- The DSST *number of correct symbols* increased (improved) by approximately 8 points in all 3 treatment groups at Week 8.
- In the comparison between vortioxetine adjunctive treatment and SSRI monotherapy in the DSST *number of correct symbols* at Week 8 (primary endpoint) a small numerical difference was observed. As the p-value for the primary endpoint was >0.05, the testing strategy was stopped. In the comparison between vortioxetine monotherapy and SSRI monotherapy, the mean difference was numerically in favour of vortioxetine monotherapy; the difference was not statistically significant. In the comparison of vortioxetine monotherapy *versus* vortioxetine adjunctive treatment the mean difference was numerically in favour of vortioxetine monotherapy; the difference was not statistically significant.
- The UPSA-B total score increased (improved) in all treatment groups after 8 weeks of treatment. The mean difference to SSRI monotherapy in the UPSA-B total score at Week 8 was numerically in favour of vortioxetine adjunctive treatment and numerically in favour vortioxetine monotherapy; the differences were not statistically significant relative to SSRI monotherapy. The standardised effect size for the UPSA-B total score at Week 8 was 0.14 in the vortioxetine adjunctive treatment group *versus* SSRI monotherapy and 0.25 in the vortioxetine monotherapy group *versus* SSRI monotherapy. The mean difference to vortioxetine adjunctive treatment in the UPSA-B total score at Week 8 was numerically in favour of vortioxetine monotherapy *versus* vortioxetine adjunctive treatment; the difference was not statistically significant.

Cognitive Function

- The mean scores of the majority of the neuropsychological tests improved from baseline to Weeks 1 and 8 in all treatment groups.
- In the comparison of vortioxetine adjunctive treatment *versus* SSRI monotherapy at Week 8, the mean differences for all the cognitive performance variables, including the overall cognition composite score, were numerically in favour of vortioxetine adjunctive treatment *versus* SSRI monotherapy (except for RAVLT acquisition and delayed recall, CRT, and STROOP incongruent). The standardised effect sizes for vortioxetine adjunctive treatment *versus* SSRI monotherapy ranged from -0.27 to 0.31.
- In the comparison of vortioxetine monotherapy *versus* SSRI monotherapy at Week 8, the mean differences in all the cognitive performance variables, except for RAVLT delayed recall, were numerically in favour of vortioxetine monotherapy. These differences were not statistically significant relative to SSRI monotherapy. The standardised effect sizes for vortioxetine monotherapy *versus* SSRI monotherapy ranged from -0.07 to 0.56.

Efficacy Results (continued)

- In the comparison of vortioxetine monotherapy *versus* vortioxetine adjunctive treatment at Week 8, the mean differences in the majority of the cognitive performance variables were numerically in favour of vortioxetine monotherapy (except STROOP congruent and incongruent). The differences were not statistically significant.
- The patients in all treatment groups reported an improvement in self-perceived cognitive function, as measured using the PDQ-D. The mean differences in the PDQ-D total score at Week 8 were numerically in favour of vortioxetine either as adjunct treatment or as monotherapy *versus* SSRI monotherapy. Furthermore, the mean differences in the PDQ-D total score at Week 8 were numerically in favour of vortioxetine monotherapy *versus* vortioxetine adjunctive treatment. None of the differences between treatment groups were statistically significant.

Depressive Symptoms and Clinical Global Impression

- The patients in all treatment groups had low scores in the depressive symptom and clinical global impression variables ($HAM\text{-}D_{17}$ total score, CGI-S score, and CGI-I score) at baseline and which improved further during the study. The mean changes from baseline in all variable scores were numerically in favour of vortioxetine either as adjunct treatment or as monotherapy *versus* SSRI monotherapy at the majority of the weeks where assessed. Furthermore, the mean changes from baseline at Week 8 were numerically in favour of vortioxetine adjunctive treatment *versus* vortioxetine monotherapy for the $HAM\text{-}D_{17}$ total score and the CGI-S score. None of the differences between treatment groups were statistically significant.

Functionality

- In addition to the UPSA-B, functionality was also assessed using the clinician-rated FAST and SDS.
- The patients in all treatment groups showed improvements from baseline in the FAST total score. The mean differences in the FAST total score at Week 8 were numerically in favour of vortioxetine either as adjunct treatment or as monotherapy *versus* SSRI monotherapy. Furthermore, the mean differences at Week 8 were numerically in favour of vortioxetine adjunctive treatment *versus* vortioxetine monotherapy. None of the differences between treatment groups were statistically significant.
- The patients in all treatment groups showed improvements in the SDS total score, which assesses overall functioning as reported by the patients. The mean differences at Week 8 were numerically in favour of vortioxetine either as adjunct treatment or as monotherapy *versus* SSRI monotherapy. Furthermore, the mean differences at Week 8 were numerically in favour of vortioxetine monotherapy *versus* vortioxetine adjunctive treatment. None of the differences between treatment groups were statistically significant.

Positive Affect

- In the CPAS-SR total score, which assesses positive affect, the patients in all treatment groups showed improvements relative to baseline. None of the differences between treatment groups were statistically significant.

Safety Results

- The adverse event incidence in the Entire Study Period is summarised below:

	VOR 10-20mg		SSRI		VOR 10-20mg+SSRI	
	n	(%)	n	(%)	n	(%)
Patients treated	50		49		52	
Patients who died	0		0		0	
Patients with treatment-emergent serious AEs (SAEs)	0		0		0	
Patients with treatment-emergent adverse events (TEAEs)	35	70.0	16	32.7	36	69.2
Total number of SAEs	0		0		0	
Total number of TEAEs	75		33		71	
Total number of AEs leading to withdrawal	1		2		3	

- No SAEs occured during the study.
- The incidence of TEAEs in the Entire Study Period was higher in the vortioxetine adjunctive treatment (69%) and vortioxetine monotherapy (70%) groups than in the SSRI monotherapy group (33%).
- The incidence of TEAEs in the Core Treatment Period was 69% in the vortioxetine adjunctive treatment group, 68% in the vortioxetine monotherapy group, and 31% in the SSRI monotherapy group.
- Three patients (6%) in the vortioxetine adjunctive treatment, 1 patient (2%) in the vortioxetine monotherapy group, and 2 patients (4%) in the SSRI monotherapy group had adverse events leading to withdrawal. Apart from nausea (which occurred in 2 patients in the vortioxetine monotherapy group), the adverse events leading to withdrawal were single events reported in individual patients.
- During the Core Treatment Period, the TEAEs with an incidence ≥5% and with a higher incidence in the vortioxetine adjunctive treatment group than in the SSRI monotherapy group were nausea, headache, *diarrhoea*, *fatigue*, *insomnia*, and *restlessness*. The TEAEs with an incidence ≥5% and with a higher incidence in the vortioxetine monotherapy group than in the SSRI monotherapy group were*nausea*, *diarrhoea*, *dizziness*, and *hyperhidrosis*.
- In both vortioxetine treatment groups, the majority of the patients with TEAEs had *mild* or *moderate* TEAEs, while in the SSRI monotherapy group, all TEAEs were either *mild* or *moderate*. The incidence of *severe* TEAEs was low, 3.8% (2 patients) in the in the vortioxetine adjunctive treatment group, 2.0% (1 patient) in the vortioxetine monotherapy group.
- The overall incidence of related adverse events was 62% in the vortioxetine adjunctive treatment group, 60% in the vortioxetine monotherapy group, and 18% in the SSRI monotherapy group.
- The incidence of TEAEs related to *insomnia* was higher in the vortioxetine adjunctive treatment (5.8%) and vortioxetine monotherapy (8.0%) groups, as compared to the SSRI monotherapy group (2.0%).
- The incidence of TEAEs related to sexual dysfunction was low; 2 patients in the SSRI monotherapy group (4.1%) had *libido decreased* and none of the patients in the vortioxetine adjunctive treatment or vortioxetine monotherapy groups had TEAEs related to sexual dysfunction.
- No clinically relevant mean changes in clinical safety laboratory test values, weight, vital signs, or ECG values were seen, and the incidence of PCS values were generally low and comparable between the treatment groups. Any differences between the treatment groups in the incidence of PCS high or PCS low values were not considered clinically relevant.
- None of the patients in any of the treatment groups had suicidal ideation or suicidal ideation at baseline or during the study.

Conclusions

- Based on the pre-specified testing strategy, treatment with vortioxetine as adjunctive therapy to current SSRI monotherapy did not reach statistical significance for the primary efficacy endpoint, change from baseline in DSST at Week 8, relative to SSRI monotherapy in patients who were in full or partial remission from MDE. None of the comparisons reached statistical significance.
- In general, vortioxetine either as adjunct treatment or as monotherapy was numerically better than SSRI monotherapy in improving a range of objective neuropsychological tests, as well as subjective patient-reported cognitive function outcome, as well as in improving clinical global impression and functionality. The effect on neuropsychological tests was more pronounced for vortioxetine monotherapy. In addition, vortioxetine adjunctive treatment was numerically better than the other treatment groups in maintaining or even further improving depressive symptoms.
- Both vortioxetine adjunctive treatment and vortioxetine monotherapy were safe and well tolerated in this study.

Report Date

15 December 2016

This study was conducted in compliance with the principles of *Good Clinical Practice*.